Automated Breast Density: Necessary or Not?

Rachel F. Brem, MD, FACR, FSBI
Professor and Vice Chair, Department of Radiology
Director, Breast Imaging and Intervention
The George Washington University
Washington, DC
Disclosure

- iCAD - Board of Directors and stockholder
Breast Density

• “Density”: That part of the breast composed of glandular and connective tissue.
• “Increased breast density”: when the ratio of dense breast tissue to fat.
Breast Density

• Fibroglandular tissue
  – Epithelial glandular tissue
    • TDLU
    • Ducts
  – Stromal elements
    • Fibrous connective tissue
      – Inter and introlobular stroma

• The rest of the breast is fat
Why is Breast Density Important

• Impact on mammography
• Impact on breast cancer risk
• Impact on breast cancer recurrence
• Impact on legislation
Breast Cancer Screening

• Screening mammography is a proven approach to breast cancer mortality reduction
  – Breast cancer mortality reduction ranges from 20-44%
Mammography in women with fatty breast tissue

- Mammography detects 98% of breast cancer in women with predominantly fatty breast tissue
Breast Density: Impact on Screening

- Effectiveness of Screening Mammography
  - All Women
    - Sensitivity: 85%
    - Proven mortality reduction
  - Women with Dense Breasts
    - Sensitivity 65%
    - More than 1/3 of breast cancers not mammographically visible in women with dense breasts
Mammograms and breast density

• 36,000,000 mammograms performed in the United States this year
• With 40% of mammograms performed in women with dense breast tissue
• 14,400,000 mammograms will be performed in women with dense breast tissue
Breast Density and Cancer Risk

• Breast Density is an Independent Risk Factor for Developing Breast Cancer\(^1\)
  – 1.9-6 x increased risk of breast cancer
  – Cancers detected in women with dense breasts are
    • larger,
    • higher grade and
    • more frequently node positive

Breast density is an independent risk factor for breast cancer

- Boyd et al (2007) carried out three nested case-controlled studies in screening populations with 1112 matched case-control pairs.
  - Women with at least 75% mammographic density had an increased risk of breast cancer compared with women with less than 10% mammographic density (odds ratio, 4.7; 95% CI, 2.0-6.2)
  - This increased risk persisted for at least 8 years and was greater in younger than older women
  - In women younger than 56 years old
    - Density accounted for 50% of interval cancers found
Breast density is a moderate independent risk factor for breast cancer

• Tesic et al conducted a population-based study of 52,752 women (ages 50-69) and used logistical regression to assess density as a breast cancer risk.
  – The odds ratio for breast cancer among women with dense breasts (BIRADS 3 and 4) was 1.9 (95% CI, 1.3-2.8) after adjustment for other risk factors such as
    • Age, BMI, age at menarche and menopause, parity, use of oral contraceptives, family history, prior breast procedures, HRT (p<0.001)

Breast Density and Breast Cancer Recurrence Risk

- Independent Risk Factor for Breast Cancer Recurrence in Women Following Lumpectomy For Invasive Cancer
- Overall Recurrence: 10% in 10 years
  - 21% five year recurrence in women with > 50% breast density\(^1\)
  - 5% five year recurrence in women with 0-50% breast density\(^1\)
- 4.3 fold increased risk of recurrence in women with dense breasts\(^2\)

Breast Density and Cancer Risk

• Strong Independent Risk Factor for Recurrence After Conservative Therapy for DCIS
  – 2.8 fold increase risk of subsequent breast cancer (DCIS or Invasive)

Breast Density and Interval Cancers

• Interval cancers have worse prognosis and become more common with increasing breast density

• RR 17.8 for interval cancer among women with >75% breast density as compared with <10% breast density

• Interval cancers are larger, more frequently node positive and have a poorer prognosis

Breast Density and Age

• Significant Clinical Issue:
  – 46.0% of all women in DMIST trial\(^1\)
  – 74% of women between age 40 and 49 years\(^2\)
  – 57% of women in their 50s\(^2\)
  – 44% of women in their 60s\(^2\)
  – 36% of women in their 70s\(^2\)

• Sensitivity of Mammography in Dense Breasts = 65\(^%\)^\(^3\)
  – More than 1/3 of cancers are missed

Breast Density and Clinical Factors

Using Clinical Factors and Mammographic Breast Density to Estimate Breast Cancer Risk: Development and Validation of a New Predictive Model

• Jeffrey A. Tice, MD; Steven R. Cummings, MD; Rebecca Smith-Bindman, MD; Laura Ichikawa, MS; William E. Barlow, PhD; and Karla Kerlikowske, MD

Breast density in the U.S. (See pie chart)

- 10% of women have almost entirely fatty breasts
- 10% have extremely dense breasts
- 80% are classified into one of two middle categories

Pie chart:
- Almost entirely fatty breasts: 10%
- Heterogeneously dense breasts: 40%
- Scattered areas of fibroglandular density in breasts: 40%
Breast Density

• Impact on Mammography
• Risk of Breast Cancer
• Legislation
Breast Density and the Law
Breast Density and the Law

• 25 States
  – Indiana most recent
  – Wording of every state is slightly different
• Federal Bill before Congress
Breast Density

• Important
• How do we classify/characterize/quantitate a women’s breast density
History of Dense Tissue Classification:

- 1953 Leborgne
- 1976: Wolfe breast density classification
- 1980: Boyd classification
- 2000: BI-RADS classification
Wolfe’s Parenchymal Pattern

Wolfe identified breast density as a risk factor for breast cancer in 1976

• Analyzed 7,214 mammograms performed 1967-1973
• Devised a classification system
  – N1: primarily fatty
  – P1: ≤25% prominent ducts
  – P2: >25% prominent ducts
  – DY: dense, fibroglandular tissue
Wolfe Classification

- Included both parenchymal patterns as well as extent of density in the breast
- Risk of breast cancer increased with increasing Wolfe Classification
## Wolfe Classification

<table>
<thead>
<tr>
<th>Wolfe Pattern</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>N1</td>
<td>Parenchyma composed primarily of fat with at most small amounts of &quot;dysplasia&quot;. No ducts visible.</td>
</tr>
<tr>
<td>P1</td>
<td>Parenchyma chiefly fat with prominent ducts in anterior portion occupying up to 25% of the volume of the breast. There may be a thin band of ducts extending into a quadrant.</td>
</tr>
<tr>
<td>P2</td>
<td>Severe involvement with prominent duct pattern occupying more than 25% of the volume of breast.</td>
</tr>
<tr>
<td>DY</td>
<td>Severe involvement with &quot;dysplasia&quot;, often describes an underlying prominent duct pattern.</td>
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Boyd Classification

<table>
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<tr>
<th>Relative risk</th>
<th>None</th>
<th>&lt;10%</th>
<th>10–25%</th>
<th>25–50%</th>
<th>50–75%</th>
<th>&gt;75%</th>
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<tbody>
<tr>
<td>Value</td>
<td>1</td>
<td>1.2</td>
<td>2.2</td>
<td>2.4</td>
<td>3.4</td>
<td>5.3</td>
</tr>
</tbody>
</table>
Breast Density: BI-RADS Lexicon

- BIRADS Lexicon 4th edition
  - Breast Density defined by amount of breast tissue in quartiles for each of the four density categories
    1. <25% glandular
    2. 25%-50% glandular
    3. 51%-75% glandular
    4. >75% glandular
BI-RADS Breast Density is a Qualitative / Visual Assessment (4th ed)
BI-RADS Breast Density is a Qualitative Assessment: 5th ed

- Four categories
- Overall assessment of volume of attenuating tissues
  - Indicate relative possibility that a lesion could be obscured
  - Mammographic evaluation should assess “the volume of attenuating tissues in the breast, to help indicate the relative possibility that a lesion could be obscured by normal tissue”
- Dense region can obscure a cancer
  - Even a small dense area can obscure a cancer
- Breast Density is classified using the denser breast

BI-RADS Breast Density remains a Qualitative Assessment: 5th ed (A-D)

- **Category A**: The Breasts are almost entirely fatty
- **Category B**: There are scattered areas of fibroglandular density
  - Optional description of a few or moderate scattered areas of density can be included in a second sentence
- **Category C**: The breasts are heterogeneously dense, which may obscure small masses
  - When dense tissue is localized to one area of the breast, the location of the dense tissue can be included in a second sentence.
- **Category D**: The breasts are extremely dense which lowers the sensitivity of mammography
  - Letters so as not to be confused with the numbered BI-RADS assessment
BI-RADS A Density: Almost Entirely Fatty
BI-RADS B Density: Scattered Areas of fibroglandular Density (subtle change in wording)
BI-RADS B Density: Scattered Areas of fibroglandular Density (subtle change in wording)
BI-RADS C Density: Heterogeneously dense which may obscure masses
BI-RADS C Density: Heterogeneously dense which may obscure masses
BI-RADS D Density: Breasts are extremely dense
Accuracy and Variability in Density Classification

• Classification is subjective
• Significant inter and intra-observer variability in density assessment
• Nicholson et al found 49% inter-observer agreement with agreement most frequently in the extremes of breast density (fatty and extremely dense)
• Kerlikowske et al demonstrated limited inter-observer agreement ($\kappa=0.59$) and moderate intra-observer agreement ($\kappa=0.72$)
Breast Density

- Important in breast cancer risk
- Important in mammographic visualization of breast cancer
- Important Legislative issue with women characterized as dense or non-dense
- Yet: subjective assessment of breast density with substantial variability is assessment and limited reproducibility
Breast Density and Clinical Factors

Using Clinical Factors and Mammographic Breast Density to Estimate Breast Cancer Risk: Development and Validation of a New Predictive Model

• Jeffrey A. Tice, MD; Steven R. Cummings, MD; Rebecca Smith-Bindman, MD; Laura Ichikawa, MS; William E. Barlow, PhD; and Karla Kerlikowske, MD Ann Intern Med. 4 March 2008;148(5):337-347
Consistency in Breast Density Assessment

• It’s not possible to be accurate and consistent when using Subjective analysis. Radiologists disagree on BI-RADS breast density
  • Radiologist preference
  • Viewing environments viewing stations and post processing, alter the appearance of density
  • Daily patient mix

• Need reliable reproducible method to determine breast density
The radiologist and breast density

- Increasingly the radiologist is the contact point with both patients and referring physicians
- Risk Assessment models will likely be using breast density
  - reliable and consistent density measurements are necessary
- Need for additional screening for women with dense breast tissue, i.e. US or MRI
Automated/ Quantitative determination of Density

- Advantages of automated reporting
  - Standardization
  - Objective assessment
  - Reproducible
  - Quantitative information used to help assign risk
Quantitative Breast Density Assessment

• Area (2 D)
• Volume (3D)
• Appearance Based
Quantitative Assessment : 2 D

• More reproducible
• Dividing the calculated area of the fibroglandular tissue by the calculated total breast area
Area Breast Density Measurement

• (2D) Planimetry
  – Described by Wolfe et al in 1987
  – Acetate overlays film; outline breast and breast tissue
    • Labor intensive
    • Does not account for inhomogeneous breast tissue win the region of interest
    • Intrinsic inaccuracies
    • Analog films: 70-94% reproducible
Area-based Methods for Density Measurement

- Uses projected area of the dense tissue as relative estimates of the volumes
- These methods generate a breast density in the range of 0-100%
- ACR BIRADS density categories are assigned in quartiles of 25% (BIRADS 1-4)
- CIRCA 1976 – still in practice today
- Very Subjective
Computerized Planimetry (Cumulus Method)

- Computerized planimeter
- Semi-automated
- Uses interactive grey scale thresholding of digitized mammograms
  - User determination of what gray scale threshold constitutes fibroglandular tissue
  - Computer determines skin and area of breast tissue as well as percentage of fibroglandular tissue based on gray scale threshold set
  - Percentage of dense breast tissue is calculated by dividing the area of fibroglandular tissue by the area of the breast
- Digital films: >90% reproducible
Figure 3. Discrepancy between reader-assigned Breast Imaging Reporting and Data System (BI-RADS) mammographic density category and quantitative mammographic density definition. Left craniocaudal mammogram read as scattered fibroglandular densities by all three readers (a). Quantitative assessment using interactive thresholding (b) yields mammographic density of 4.6%, which is well below the BI-RADS definition of 25%-50% dense for the scattered fibroglandular density category (1).
**AutoDensity**: an automated method to measure mammographic breast density that predicts breast cancer risk and screening outcomes

Nickson et al.
Computerized 2 D Assessment of Breast Density

- Reduce variability of interpretation
- Still measuring 3D object in 2D projections
- Impacted by:
  - Breast positioning
    - Greater retrogladular fat will decrease breast density measurement
“We further recognize that both subjective estimates and planimetry measurements of breast density based on area as depicted on (2-D) mammograms are imprecise indicators of the volume of dense tissue”
Need for measure of 3D density for 3D breast

- Methods to determine 3D volume from 2D mammo
  - Evaluate more than amount of dense tissue
  - Look at algorithmic feature of the density
  - **BASED ON 2D IMAGE**
    - 3D DATA IS EXTRAPOLATION OF INFORMATION ON MAMMO
- Develop 3D map
- Integrate features of the tissue into determination of 3D density- bit based on 2D data
- 3 Commercially available products
  - Quantra (Hologic)
  - Volpara (Matakina)
  - iReveal (iCAD)
Area-based Methods for Density Measurement

<table>
<thead>
<tr>
<th></th>
<th>Area:</th>
<th>Volumetric:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
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<td>5%</td>
</tr>
<tr>
<td></td>
<td>5%</td>
<td>12%</td>
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</table>
Area-based Methods for Density Measurement

<table>
<thead>
<tr>
<th></th>
<th>Area 0%</th>
<th>Volumetric 0%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50%</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>24%</td>
</tr>
</tbody>
</table>

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Volumetric vs. Area Density

\[
\frac{4L \times 2L}{4L \times 2L} \times 100\% = 100\%
\]

\[
\frac{4L \times 2L \times 0.2L}{4L \times 2L \times 2L} \times 100\% = 10\%
\]
Determine Density Volume from 2D Mammograms

- Algorithms developed to estimate 3D volume from 2D Mammograms
- No definitive correlation that better than 2D
- Correlations to MRI parenchyma
Breast Density Measurement

• Automated *volumetric computation from* digital mammography
  – Volumetric breast density = volume of fibroglandular tissue (FBT) divided by volume of FBT and fat
  – correlation with MRI

Volume-based Methods for Density Measurement

- Utilizes volumetric measurement of the dense tissue and the volume of the breast
- These methods typically generate a breast density in the range of 0 - 35%
- Quantitative
Volpara v1.5.7
Breast Density Assessment

<table>
<thead>
<tr>
<th></th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of Fibroglandular Tissue (cm³)</td>
<td>24.4</td>
<td>22.4</td>
</tr>
<tr>
<td>Volume of Breast (cm³)</td>
<td>685.5</td>
<td>694.8</td>
</tr>
<tr>
<td>Volumetric Breast Density (%)</td>
<td>4.4</td>
<td>4.7</td>
</tr>
<tr>
<td>VDG(R) / BI-RADS(R) Breast Density</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>
Quantra (Hologic)

• Algorithm that objectively provides breast composition information
• This information includes the Quantra Density Category which is consistent with the four breast composition categories of the ACR BI-RADS® Atlas, Fifth Edition
Quantra Software Results

Quantra provides measures of:
- Volume of dense tissue - $V_{fg}$
- Volume of breast tissue - $V_{b}$
- A percentage value of breast density based upon calculations using the previous values - $V_{bd}$

Other information provided includes:
- $Q_{abd}$ a BI-RADS®-like integer value for breast tissue composition
Quantra Software Secondary Capture Displays

- **Quantra Volumetric Breast Density Assessment**
- **Patient Name:** 21461843
  **Patient ID:** 21461843
  **DOB (Age):** 1 Jan 1962 (52)
  **Study Date:** 18 Aug 2014

- **Quantra Breast Density Category:** b: scattered areas of fibroglandular density

- **Volumetric Breast Density - Average:**
  - **Right:** 206
  - **Left:** 183
  - **Vd:** Volume of dense tissue (cm³)
  - **Vb:** Volume of breast (cm³)
  - **Vbd:** Volumetric breast density
  - **Vbd:** Volumetric breast density - Average
  - **QDC:** Quantra Breast Density Category

- **Version:** 2.1.1

- **Quantra 3D Volumetric Breast Density Assessment**
- **Patient Name:** 00400132
  **Patient ID:** 00400132
  **DOB (Age):** 1 Jan 2008 (6)
  **Study Date:** 25 Aug 2008

- **Quantra Breast Density Category:** b: scattered areas of fibroglandular density

- **Volumetric Breast Density - Average:**
  - **Right:** 67
  - **Left:** 96
  - **Vd:** Volume of dense tissue (cm³)
  - **Vb:** Volume of breast (cm³)
  - **Vbd:** Volumetric breast density
  - **Vbd:** Volumetric breast density - Average
  - **QDC:** Quantra Breast Density Category

- **Version:** 2.1.1
iReveal (iCAD) Automated Breast Density Analysis Process

- iReveal analyzes the structure, texture, and dispersion of the tissue
  - Total breast area
  - Dense area (dense fibroglandular tissue)
  - Percent breast density
  - Tissue Characterization
  - Dispersion

- Analyzes a mammogram to find dense areas that may mask cancer

- Converts percentage to density category calibrated to BI-RADS standard
Breast B may have a higher percentage of dense breast tissue calculated by volume, but Breast A has the greater chance of obscuring a cancerous lesion.

The dense structure in A is more likely to hide a cancerous lesion by reducing the ability to visualize fine structures and details that could be a sign of a malignant abnormality. In this example, dispersion, in combination with percent breast density, best depicts results congruent with an expert radiologist’s interpretation of breast density.
Appearance-based

- BI-RADS categories are defined not only by the percentage of the breast covered by dense tissue, but also by the dispersion of this tissue throughout the breast.

- The iReveal approach assesses breast density by examining the mammographic texture and appearance of the dense tissue, emulating - quantitatively - the approach of BI-RADS.
iReveal Automated Breast Density Score Card

**Patient Demographics**
- **Patient Name:** Julie Wilson
- **Patient ID:** A4023B85FFC7DCAB4C53F367B4DEAD6D
- **Patient DOB:** 01/01/1944
- **Accession #:** 999
- **Study Date:** 09/29/2014 12:11:23 PM

**iReveal Results**
- **Breast Area (cm²):** Right 297, Left 266
- **Fibroglandular Tissue Area (cm²):** Right 2, Left 3
- **Breast Density (%):** Right 1, Left 1
- **iReveal Density Category:** A

**Patient Demographics**
- **Patient Name:** Jane Doe
- **Patient ID:** CAD0000060
- **Patient DOB:** 01/02/1934
- **Accession #:** 8675309
- **Study Date:** 01/06/2000 09:28:15 AM

**iReveal Results**
- **Breast Area (cm²):** Right 214, Left 197
- **Fibroglandular Tissue Area (cm²):** Right 64, Left 59
- **Breast Density (%):** Right 30, Left 30
- **iReveal Density Category:** B

**Patient Demographics**
- **Patient Name:** Susan Jones
- **Patient ID:** CAD000067
- **Patient DOB:** 07/27/1941
- **Accession #:**
- **Study Date:** 01/24/2000 2:46:04 PM

**iReveal Results**
- **Breast Area (cm²):** Right 128, Left 109
- **Fibroglandular Tissue Area (cm²):** Right 71, Left 66
- **Breast Density (%):** Right 56, Left 60
- **iReveal Density Category:** C

**Patient Demographics**
- **Patient Name:** Mary Smith
- **Patient ID:** CE09000036
- **Patient DOB:** 10/20/1934
- **Accession #:** 0001153824
- **Study Date:** 05/15/2014 11:52:36 AM

**iReveal Results**
- **Breast Area (cm²):** Right 97, Left 107
- **Fibroglandular Tissue Area (cm²):** Right 59, Left 69
- **Breast Density (%):** Right 60, Left 64
- **iReveal Density Category:** D
Breast Density Assessment and Tomosynthesis

- Improved ability to determine 3D breast density from 3D data with extrapolation
- No commercially available product
- Under development
Fully Automated Quantitative Estimation of Volumetric Breast Density from Digital Breast Tomosynthesis Images: Preliminary Results and Comparison with Digital Mammography and MR Imaging

Pertuz S, McDonald ES, Weinstein SP, Conant EF, Kontos D. Radiology: 2015; 279(1); 65-74.
Figure 3: Scatterplots for VBD estimates (a) per breast and (b) per side. Linear regression lines, along with related r values, show high agreement. CC = craniocaudal, MLO = mediolateral oblique.
Table 1

<table>
<thead>
<tr>
<th>Reader No.</th>
<th>Percentage Fibroglandular Tissue for Reader 2 (%)</th>
<th>Percentage Fibroglandular Tissue for Reader 3 (%)</th>
<th>Percentage Fibroglandular Tissue with the Automated Method (%)</th>
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</thead>
<tbody>
<tr>
<td>Reader 1</td>
<td>0.96 (0.94, 0.98)</td>
<td>0.96 (0.93, 0.98)</td>
<td>0.92 (0.88, 0.96)</td>
</tr>
<tr>
<td>Reader 2</td>
<td>…</td>
<td>0.97 (0.95, 0.99)</td>
<td>0.96 (0.93, 0.98)</td>
</tr>
<tr>
<td>Reader 3</td>
<td>…</td>
<td>…</td>
<td>0.97 (0.94, 0.98)</td>
</tr>
</tbody>
</table>

Note.—Numbers in parentheses are 95% CIs.
Figure 4

Box plots used to compare VBD estimates from FFDM, MR imaging, and DBT images. (a) VBD estimates from FFDM are significantly different than those from DBT and MR imaging. Estimates from MR imaging and DBT are not significantly different. (b) Total breast volume estimates are not significantly different. (c) Absolute fibroglandular tissue volume estimates from FFDM are significantly different than those from DBT and MR imaging. Estimates from MR imaging and DBT are not significantly different. FGT = fibroglandular tissue volume.

Breast Density and Tomosynthesis

• Determine 3D density from 3D image
• Correlation to MRI parenchyma
• Inter-observer agreement and consistency
• Preliminary data
BREAST DENSITY

• Increased risk for breast cancer
  – Varying relative risk in different studies

• Limits detection of breast cancer with mammography
  – Other modalities not affected by breast density
    • MRI, BSGI, Ultrasound

• Political issue
  – Inform law
  – Insurance coverage
  – Media coverage
  – Right of women to know
Breast Density

• Standard subjective BI-RADS determination is inconsistent with inter and intra-observer variability

• Increasing importance and use to determine limitations of mammography as well as breast cancer risk

• Must develop methods to accurately and consistently determine breast density
  – Radiologists are the initial and often primary “face” of information to patients regarding breast density
  – Accurate assessment for optimal discussion with referring physicians

• Use of breast density in risk assessment models
  – Surveillance with adjunct imaging modalities (MRI, BSGI)
  – Accurate conveyance of density/risk to referring physicians and genetic counselors
Breast Density

• Must have reliable, reproducible method to determine breast density
• Must have automated, accurate breast density determination
• Currently 2D/ pseudo 3D
• With tomosynthesis opportunity for more accurate 3D density determination
  – Remains a work in progress